Diastolic Dysfunction in Pediatric Cardiac Patients: Evaluation and Management

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Opinion statement

The heart is a complex and sophisticated pump that cycles between two phases: diastole, during which a compliant chamber (ventricle) allows the blood to fill from a reservoir chamber (atrium) of low pressure, and systole, during which a stiff chamber with rapidly rising pressure ejects the blood into an arterial circuit of high pressure. However, the systolic and diastolic cycles are not dichotomous. They have complex interactions with interrelated segments of the cardiac cycle. Although the entity of "diastolic heart failure with preserved systolic function" has been applied in adult patients, a discrete diagnosis of systolic and diastolic heart failure may be difficult to apply in pediatric patients. Advances in echocardiography have helped decipher the morphologic and physiologic expression of congenital and acquired heart disease and have increased our understanding the diastolic function and dysfunction. The evolving concept of systolic and diastolic heart failure is helping us develop a strategy for its management in pediatric patients with complex heart diseases.

Introduction

Approximately half the adult patients with newly diagnosed heart failure have "diastolic heart failure" with preserved systolic function [1]. The prevalence of diastolic heart failure in pediatric patients with congenital and acquired heart diseases is unknown, perhaps because a paradigm of discrete diagnosis of systolic and diastolic heart failure may be difficult to apply in pediatric patients. The congenital heart diseases and cardiomyopathies in pediatric patients entail hemodynamic overloads that have complex interactions with interrelated segments of the cardiac cycle. Nevertheless, the assessment of ventricular diastolic function and filling pressures is of clinical importance in order to differentiate this syndrome from other diseases and to identify the underlying pathologic process, so as to institute the best possible treatment. Over the past decade, advances in echo-Doppler have helped decipher the morphologic and physiologic expression of congenital and acquired heart disease and have increased our understanding of diastolic function and dysfunction. The purpose of this article is to present the current understanding of diastology, the application of echo-Doppler measures of diastolic function to the treatment regime, and advances in therapeutic intervention for diastolic dysfunction.

Physiology of diastole

During diastole, the myocardium, after contraction, returns to its unstressed length and force. The process is orchestrated by [2••]:

- Myofiber architecture
- Electrical sequence
- Mechanical sequence

The myoarchitecture of the left ventricle has a helical arrangement of myofibers, with the subendocardial layer composed in the form of a right-handed helix, gradually evolving into a left-handed helical fiber orientation in the subepicardial layer [3,4,5]. The left ventricular (LV) fiber orientation is a function of transmural location, with the fiber direction predominantly longitudinal in the endocardial and epicardial surfaces and circumferential in the midwall because of the continuously changing helical angle between the endocardium and epicardium [5,6].

Electrical diastole starts with apical endocardial repolarization and propagates to the basal endocardium, from which it propagates to the epicardium. The transmural electrical gradients propagate in a base-to-apex direction. Thus, the endocardial and epicardial onset of relaxation is temporally discrete, beginning in the apical subendocardium just before closure of the aortic valve, with subepicardial relaxation beginning at the base after aortic valve closure [2••,7•].

As a consequence of myofiber architecture and electrical repolarization, the mechanical sequence of relaxation of the helixes is in the direction opposite the systolic sequence, but like it, consists of a distinctive counterdirectional movement: apex to base for the subendocardium and base to apex for the subepicardium. This creates active apex-to-base and subendocardial-to-subepicardial relaxation gradients, which result in diastolic untwisting and suction.

Systole and diastole are not discrete segments of the cardiac cycle. There are tightly coordinated temporal and functional relationships between LV twist during systole, with accompanying mitral annular motion toward the apex, and the untwist and recoil that generate the negative intraventricular pressure suction in early diastole [8•,9,10]. The ventricular untwist and recoil is followed by the rapid motion of the mitral annulus back toward the base of the heart, which aids ventricular filling by moving the annulus around the column of the incoming blood [11]. Thus, LV twist is a mechanism for generating stored energy during systole,

which is released during early diastole to produce ventricular recoil, upward annular motion, and suction [12].

Subsequent to early relaxation and diastolic suction, ventricular filling with blood during late diastole is the result of many other interplaying factors, including viscoelastic forces of the myocardium (cardiomyocytes and extracellular matrix, myocardial tone, and wall thickness [13]), pericardial restraint, and ventricular interaction. Together, they determine the ventricular stiffness (inverse of ventricular compliance) that atrial contraction has to overcome for ventricular filling during the late phase of diastole.

Pathophysiology of diastolic dysfunction

Elevated ventricular filling pressure is the main pathophysiologic consequence and dyspnea on effort is the main symptom of diastolic dysfunction [14]. Diastolic dysfunction is usually viewed as a significant abnormality in active relaxation and passive stiffness of the ventricle. However, as noted earlier, systole and diastole are not discrete segments of the cardiac cycle; hence, diastolic dysfunction is not a discrete impairment of cardiac function isolated from systolic dysfunction. Studies indicate that in diastolic dysfunction, there are combined systolic and diastolic abnormalities, particularly involving ventricular twist and deformation (strain). These abnormalities lead to delayed untwisting, reduced ventricular suction, and impaired early diastolic filling, which, along with increased ventricular stiffness and impaired late diastolic filling, raise the LV end-diastolic and left atrial (LA) pressures. The mechanism of diastolic dysfunction and underlying precipitating factors are outlined in Fig. 1.

Chronic pressure overload to the left ventricle from congenital heart disease (CHD), such as LV outflow tract obstructive lesions and, less commonly, primary and secondary hypertension, leads to LV hypertrophy and decreased LV twist. This is associated with delayed LV untwist and relaxation, which reduce early diastolic filling. In the presence of normal LA pressure, this shifts a greater proportion of LV filling to late diastole after atrial contraction and increased filling pressures. Chronic pressure overload and volume overload from congenital valvular lesions may induce not only LV hypertrophy but also myocardial ischemia and fibrosis, which increase LV stiffness. Similar conditions may be seen in CHD with single-ventricle physiology; these conditions have been found to increase pressure and volume overload both before and after palliative procedures. In myocardial disease due to congenital
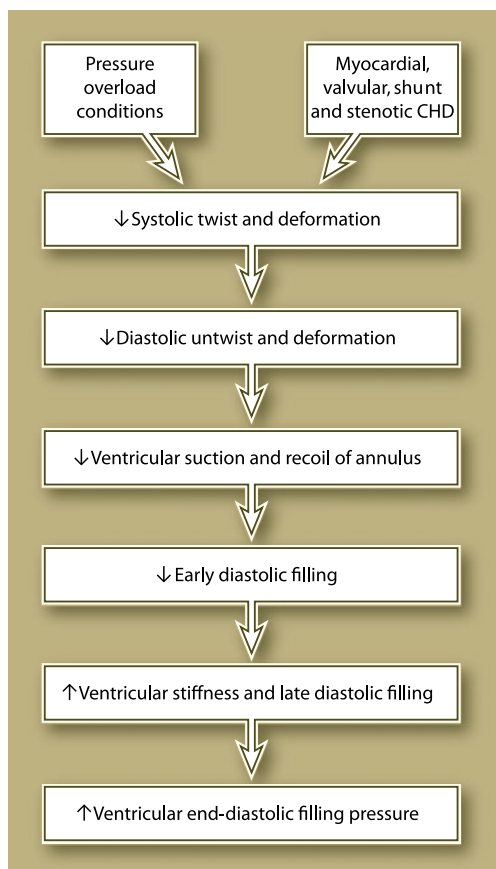
Figure 1. The mechanisms of diastolic dysfunction. CHD–congenital heart disease.

and acquired myopathies, diastolic dysfunction is commonly present. In hypertrophic cardiomyopathy, the marked variability in phenotype, muscle mass, amount of myocardial fiber disarray, and obstructive versus nonobstructive physiology results in many different combinations of altered relaxation and compliance [15••]. In restrictive cardiomyopathy, regardless of whether it is idiopathic, genetic, ischemic, or infiltrative in nature, there is increased ventricular stiffness with marked elevation in filling pressures. In dilated cardiomyopathies of idiopathic, genetic, or ischemic etiologies, there is combined systolic and diastolic dysfunction with decreased twist and deformation, delayed untwisting, reduced ventricular suction, impaired early diastolic filling, and increased ventricular stiffness, resulting in markedly elevated diastolic filling pressure.

Evaluation of diastolic function
Echocardiography has been used as the main imaging modality in the evaluation of LV diastolic function in adults and is increasingly used to evaluate diastolic function in pediatric patients with heart diseases. An approach to the evaluation of diastolic function using established and newer echocardiographic indices in pediatric patients is outlined in Fig. 2.

The chronicity of LV diastolic dysfunction is expressed as an increase in LA volume. In adult patients, "LA volume is to diastolic function as the HbA$_1$C [hemoglobin A$_{1c}$] is to diabetes" [16••]. The biplane area length or Simpson's methods may be used to measure LA volume. In adult patients with heart disease, an LA volume index greater than 34 mL/m^2 is considered an independent predictor of increased cardiac morbidity and mortality [17]. Although no such studies have come out with prognostic importance of LA volume in the pediatric population, an LA volume greater than 2 z-score for age and body surface area in the absence of chronic anemia, such as sickle cell anemia and other high-output states, and significant mitral valve disease should be viewed as the marker of LV diastolic dysfunction and potential for increased cardiac morbidity in pediatric patients [18].
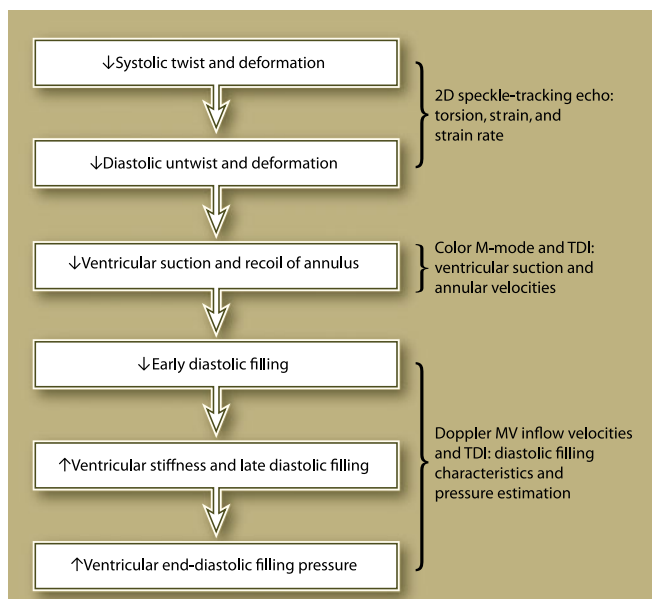
Figure 2. The different echocardiographic imaging modalities that may be used to evaluate diastolic dysfunction. 2D—two-dimensional; MV—mitral valve; TDI—tissue Doppler imaging.

An enlarged LA reflects the chronicity of LV filling pressure elevation, whereas echo-Doppler–derived LV filling dynamics and LV function at the time of measurement reflect acuity.

LV twist and untwist, strain, and strain rate

With the introduction of speckle-tracking echocardiography, it is feasible to quantify LV rotation, twist, and untwist clinically [8•,19]. Speckle within B-mode images of myocardium are "natural acoustic markers" that result from backscatter characteristics of ultrasound that can be tracked from frame to frame. Myocardial velocity and strain are obtained by automated measurement of the change in position and separation between speckle patterns over the heart cycle. Unlike tissue Doppler methods, this methodology is relatively angle independent. LV twist is calculated as the difference between basal and apical rotation measured in LV short-axis images.

Strain and strain rate reflect myocardial deformation (percentage shortening or thickening) and the rate of deformation, respectively. Significant relationships exist between the time constant of diastolic pressure decay, τ—the gold standard of diastolic measurement (measured by cardiac catheterization)—and diastolic strain rate. Strain rate is relatively load independent. Two-dimensional (2D) strains may also be measured by 2D speckle-tracking echocardiography. Thus, reduced myocardial systolic strain (Fig. 3), rotation, LV suction, longitudinal (annular) function, and delayed untwisting can all be measured by 2D speckle-tracking echocardiography [11] and can be compared with normal values for pediatric age groups [20•,21]. Although promising, the evaluation of diastolic dysfunction by deformation imaging would need additional studies to substantiate its clinical value in pediatric patients with congenital or acquired heart diseases.

Ventricular suction

Mitral-to-apical flow propagation, which represents LV suction, can be measured by the slope method. Acquisition is performed in the apical four-chamber view, using color flow imaging with a narrow color sector, and the M-mode scan line is placed through the center of the LV inflow blood column from the mitral valve to the apex. The Nyquist limit is lowered so that the central highest velocity jet is blue. Flow propagation velocity (Vp) is the slope of the first aliasing velocity during early filling, measured from the mitral valve plane into the LV cavity [22]. The Vp is relatively load independent. The normal value of Vp in the young is greater than 55 cm/s and in adults, greater than 50 cm/s. However, the complexity of intraventricular flow in congenital heart diseases and the limitations of current imaging techniques make it difficult to relate intraventricular flow patterns to LV myocardial function in a quantitative manner; therefore, they are of limited clinical value in pediatric patients.
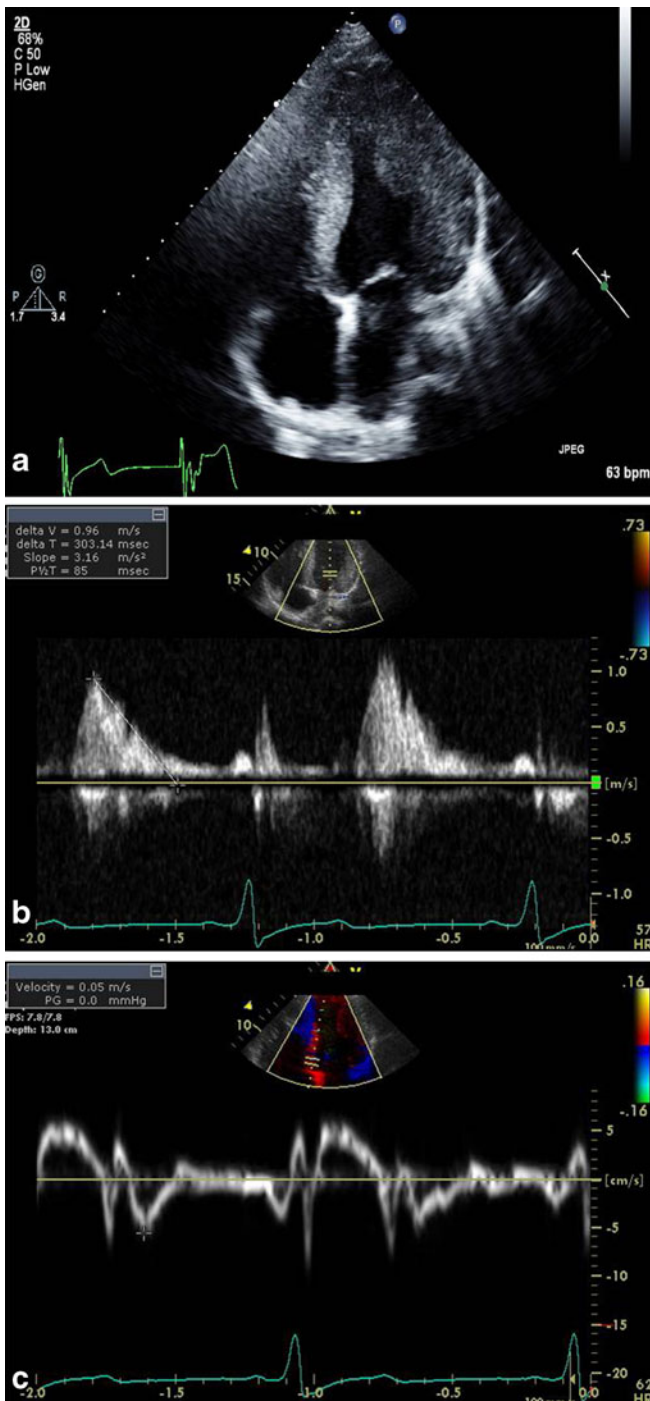
Figure 3. Evaluation of delayed relaxation abnormality and ventricular filling pressure. **a**, Two-dimensional echocardiographic four-chamber image from a pediatric patient with hypertrophic cardiomyopathy. **b**, Prolonged deceleration time (DT=303 ms) in the patient, indicating a delayed relaxation abnormality and mitral valve E velocity of 96 cm/s. **c**, Image from the same patient, showing the tissue Doppler–measured early diastolic myocardial velocity at the lateral annular site of the mitral valve (e'=5 cm/s), which is reduced for the patient's age (normal e'=10 cm/s). The calculated E/e' ratio is 19 (normal<12), indicating elevated left ventricular filling pressure.

Recoil of annulus and LV relaxation

The reduction in recoil of the mitral annulus back toward the base of the heart and LV relaxation can be characterized through the evaluation of mitral annular motion with speckle tracking and Doppler tissue imaging (DTI). Pulse-wave DTI is performed in the apical view to acquire mitral annular velocities by positioning the sampling region at or 1 cm within the septal

and lateral insertion sites of the mitral leaflets to measure the systolic (s′) and early (e′) and late (a′) diastolic velocities. Normal values of DTI-derived velocities in the pediatric population are established and are influenced by age [20•]. A significant association between e′ and LV relaxation and a minimal effect of preload on e′ in the presence of impaired LV relaxation makes it a sensitive tool to evaluate LV early diastolic dysfunction both in pediatric and adult patients [23•,24,25]. The time interval between the QRS complex and the onset of mitral E velocity, subtracted from the time interval between the QRS complex and e′ onset to derive TE-e′, can provide incremental information [15••] regarding restrictive LV filling, in which mitral E velocity occurs earlier than the onset of e′ and TE-e′ is prolonged with diastolic dysfunction. Studies have revealed that TE-e′ is strongly dependent on the time constant of LV relaxation and LV minimal pressure [26]. Thus, in the presence of impaired LV relaxation and irrespective of LA pressure, the e′ velocity is reduced and delayed and TE-e′ is prolonged and may be a sensitive tool to evaluate diastolic dysfunction in pediatric patients with congenital or acquired heart diseases (please see "Clinical Applications"). A prolonged TE-e′ may be useful for discerning delayed relaxation when e′ peak velocity is borderline or when e′ is affected by high LA pressure.

Diastolic filling characteristics: mitral valve inflow velocity profile

The mitral inflow velocity profile obtained by pulsed Doppler interrogation provides LV filling characteristics. The E velocity represents the early mitral inflow velocity and the A velocity the atrial contractile component of mitral filling. The deceleration time (DT) of the E velocity, calculated from the interval from peak E to a point of intersection of the deceleration flow with the baseline, correlates with time of pressure equalization between the left atrium and left ventricle (Fig. 3). It shortens or lengthens according to early or late equalization of LA and LV filling pressures, respectively. In fetuses, neonates, and young infants, the E velocity is less than the A velocity because of increased end-diastolic atrial contraction to overcome the ventricular stiffness normally present in this age group. With myocardial growth and maturation, E velocity increases and A velocity decreases. By 3 to 6 months of age, the E velocity is higher than the A velocity, and they, along with DT, continue the trend in the first

5 years of life to achieve the adult profile [20•]. Besides physiologic changes in cardiac growth and maturation, mitral inflow velocities are affected by changing heart rate in patients in the pediatric age group. The evaluation of diastolic dysfunction in pediatric age should take into account these physiologic changes in mitral valve (MV) flow velocity profile.

Altered MV inflow velocity characteristics due to delayed diastolic relaxation from hypertrophy, dyssynergic wall motion, and increased ventricular-arterial afterload can be detected by the presence of prolonged DT (>2 z-score for age [27•]) and reduced E/A ratio than normal for age, which result from the delay in emptying and partial compensation by a more vigorous end-diastolic atrial contraction (Fig. 3) [16••]. However, a reduced E/A ratio (usually <1) and prolonged DT (usually >240 ms) for age have high specificity for delayed LV relaxation but may be seen with either normal or increased filling pressures, depending on the degree of delayed LV relaxation. Further, in hypertrophic cardiomyopathy patients with normal systolic function (ejection fraction [EF] >50%) but delayed LV relaxation, the transmitral velocity profile may be variable [28].

With chronicity of delayed diastolic relaxation and a compensatory increase in LA pressure, the E velocity and E/A ratio may increase and the DT may shorten, resulting in pseudo-normalization of MV velocity profile. However, the e′ velocity remains reduced, identifying the underlying LV relaxation abnormality along with associated increased LA size, which can discriminate normal from pseudo-normal [24]. A restrictive pattern of diastolic dysfunction develops in time, which manifests with a short isovolumic relaxation time (IVRT), increased E/A velocity ratio (usually >2), and reduced DT (usually shorter than normal for the age group). This, in combination with an enlarged left atrium, characterizes advanced diastolic dysfunction and worse functional class. This stage is characterized with reduced e′ and a′ myocardial diastolic velocities less than 2 z-score for the age group, which is a more sensitive parameter for abnormal myocardial relaxation than mitral velocity variables (Fig. 4).

LV stiffness

Increased LV stiffness has more rapid rates of deceleration of early LV filling and shorter DTs [29]. With a relatively constant LA pressure during early LV filling, DT is proportional to the inverse square root of LV
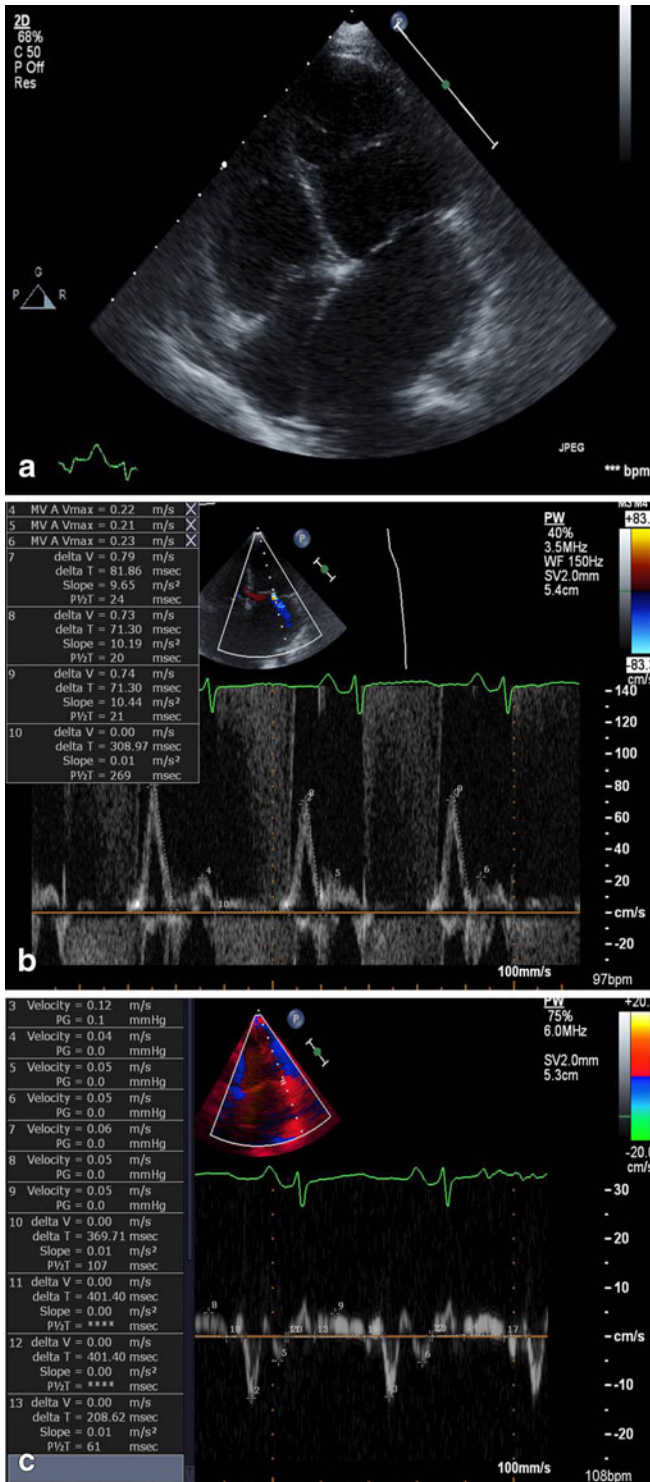
Figure 4. Evaluation of ventricular stiffness and filling pressure. **a**, Two-dimensional echocardiographic four-chamber image from an older pediatric patient with restrictive cardiomyopathy with a markedly dilated left atrium. **b**, Shortened deceleration time (DT=71 ms in the *middle panel*) in the patient, indicating a restrictive pattern and increased ventricular stiffness and a mitral valve E velocity of 79 cm/s. **c**, Image from the same patient, showing the tissue Doppler–measured early diastolic myocardial velocity at the lateral annular site of the mitral valve (e'=12 cm/s), which is borderline reduced for the patient's age (normal e' = 13 cm/s). The calculated E/e' ratio is 7 (normal<8), indicating borderline elevated left ventricular filling pressure.

stiffness [30] and can be used as a surrogate marker of LV stiffness. Normal values for different pediatric age groups have been established [27•].

LV diastolic filling pressure

Elevated LV end-diastolic filling pressure (LVEDP) is the end result of diastolic dysfunction and the determinant of symptoms such as breathlessness on exertion. The ratio of MV E velocity to DTI-derived MV annular velocity e′ (E/e′) has been used to predict LVEDP reliably [31,32]. A ratio less than 8 is usually associated with normal LVEDP, whereas a ratio greater than 15 is associated with increased LVEDP (Fig. 3) [24]. When the value is between 8 and 15, E/e′ is ambiguous in predicting the LVEDP. *T*E-e′ can be used in this situation, and an IVRT/*T*E-e′ ratio greater than 2 has been found to have reasonable accuracy in identifying adult patients with increased LVEDP [26]. Further, a study showed that the ratio of mitral E velocity to global myocardial strain rate during IVRT (by speckle tracking echocardiography; E/SR-IVRT) can predict LV filling pressure in adult patients in whom the E/e′ ratio is inconclusive [33]. No such studies have been reported in the pediatric population yet, and the clinical utility of these predictors of LV filling pressure in pediatric patients with congenital or acquired cardiac diseases needs to be substantiated.

Clinical applications

Congestive heart failure (CHF) is the most common manifestation of congenital and acquired heart diseases. Mitral inflow velocities and filling patterns, myocardial diastolic velocities, and deformation correlate better than depressed left ventricular ejection fraction (LVEF) with LV filling pressure, functional class, and prognosis in adult patients and incremental predictors in pediatric patients at risk for hospitalization, need for inotropes, transplantation, or death. Findings from studies include the following:

- In adult patients with CHF and an EF <35%, survival free of death and hospital admission was 77% when DT was greater than 125 ms, and only 18% when DT was less than 125 ms. DT was incremental to age, functional class, third heart sound, EF, and LA area in this population [34].
- Among adult patients with dilated cardiomyopathy (DCM), survival of those with persistent

restrictive diastolic dysfunction at 1, 2, and 4 years (65%, 46%, and 13%) was significantly lower than that of patients with reversible restrictive and nonrestrictive diastolic dysfunction (100% at 1 and 2 years and 97% at 4 years, respectively) [35].

- In another study of adult patients with ischemic cardiomyopathy and DCM, survival of patients at 40 months was 72% with a′ greater than 5 cm/s and 22% with a′ less than 5 cm/s; on multiple regression, a′ less than 5 cm/s, E/e′ greater than 15, and DT less than 140 ms were independent predictors of events [36].
- In adult patients with hypertension, e′ less than 3.5 cm/s was the most powerful independent predictor of cardiac death and transplantation [37].
- In pediatric patients status post tetralogy of Fallot, those with e′/a′ less than 1 at the lateral annulus of the tricuspid valve and at the septum had a longer QRS and greater QRS, QT, and JT dispersion, which are risk factors for heart failure and sudden cardiac death [38].
- In pediatric patients with DCM, compared with normal subjects, a decreased tricuspid e′ velocity (<8.5 cm/s) was a better predictor than LVEF of those at risk for hospitalization, need for inotropes, transplantation, or death [39].
- In children with noncompacted DCM, lateral mitral e′ velocity was reported to be the most sensitive and specific predictor of the primary end point [40].
- In children with hypertrophic cardiomyopathy, the mitral E/septal e′ ratio predicted which patients were at risk for adverse clinical outcomes including death, cardiac arrest, ventricular tachycardia, and decreased exercise tolerance [41].

Indications for hospitalization

Indications for hospitalization are:

- Change in functional status
- Progressive dyspnea on exertion
- Congestive heart failure
- Arrhythmias

Treatment

Specific therapeutic measures

- In pediatric patients with congenital, acquired, and myopathic heart diseases presenting with the clinical syndrome of CHF, the treatment should be directed at the underlying etiology and precipitant causes (Fig. 2) and individualizing the therapeutic approach.
- Those who have valvular heart disease causing volume overload requiring early intervention, such as in status post tetralogy of Fallot with free pulmonary regurgitation causing right ventricular and LV diastolic dysfunction, would benefit from a pulmonary valve replacement. A similar strategy should be used for LV dysfunction from chronic aortic regurgitation. Pediatric patients with LV outflow tract obstructive lesions causing LV hypertrophy and dysfunction would benefit from surgical relief of the mechanical obstruction. Restrictive cardiomyopathy requires symptomatic treatment and cardiac transplantation, whereas patients with hypertrophic cardiomyopathy will have improved quality of life and survival from pharmacotherapy, relief of outflow obstruction, and internal cardiac defibrillator placement.

General therapeutic measures

- Because of the paucity of large interventional studies in pediatric patients with CHF, an evidence-based approach to treatment is lacking; hence, a clinical judgment-based approach to management of patients with diastolic dysfunction is often undertaken.
- General therapies are used to favorably manipulate hemodynamics to help better control symptoms. For diastolic dysfunction due to delayed relaxation and recoil, the duration of diastole is critical, and β-blockers or rate-slowing calcium channel blockers often provide symptomatic response, allowing more time for failing diastole to complete its work.

Rate-slowing calcium channel blockers

- Calcium channel blockers bind the L-type calcium channels located on the vascular smooth muscle, cardiac myocytes, and cardiac nodal tissue. Rate-slowing calcium channel blockers bind with nodal tissue for their effect.
- *Contraindications*: Hypersensitivity to the drug is a contraindication to therapy.
- *Main drug interactions*: Because of its involvement in the cytochrome P-450 enzyme system (substrate and inhibitor), this group of drugs interacts with other medications metabolized by the same enzyme systems, including azole antifungals, tacrolimus, cyclosporine, phenobarbital, rifampin, and carbamazepine.

Nondihydropyridines

- *Special note*: The two agents in this subclass, verapamil and diltiazem, are used mainly for rate-limiting effects. They are less potent vasodilators.

Diltiazem

Standard dosage	1.5 to 2 mg/kg/d by mouth one or two times per day using an extended/sustained-release product.
Contraindications	Hypersensitivity to the drug or any component is a contraindication to therapy. Use with caution in patients with advanced heart block or patients already receiving a β-blocker.
Special note	Extended/sustained-release products usually are used for treatment.
Cost/cost-effectiveness	Extended-release tablets cost between $1.50 and $2.50 per tablet. A regimen of 180 mg once a day would cost approximately $550 to $915 per year.

Dihydropyridines

- Nifedipine, amlodipine, felodipine, and nicardipine generally are not used for rate-limiting effects; they are used mainly as antihypertensives.

β-Blockers

- The safety and efficacy of some β-blockers, such as metoprolol, have been established in the pediatric population [42].
- *Contraindications*: Advanced heart block, uncompensated heart failure, and hypersensitivity to β-blockers are contraindications for therapy. Use with caution in patients with diabetes mellitus, hyperthyroidism, pheochromocytoma, or bronchial asthma or obstructive airway disease.
- *Main drug interactions*: Angiotensin-converting enzyme (ACE) inhibitors, digoxin, diltiazem, flecainide, hydralazine, prazosin, quinidine, monoamine oxidase inhibitors, tricyclic antidepressants, haloperidol, and verapamil may cause additive cardiovascular effects when given with β-blockers.
- *Main side effects*: Bradycardia, chest pain, depression, dizziness, fatigue, lethargy.

Atenolol

Standard dosage	0.5 to 1 mg/kg/d by mouth, with a maximum dosage of 2 mg/kg/d, not to exceed 100 mg/d.
Cost/cost-effectiveness	Generic forms cost $0.80 per tablet or $300 per year using a dose of 25 mg once a day.

Propranolol

Standard dosage	Initial dosage of 0.5 to 1 mg/kg/d in divided doses every 6 to 12 hours, increased gradually to a dosage of 1 to 5 mg/kg/d to a maximum of 8 mg/kg/d.

Cost/cost-effectiveness	The oral formula, at a dosage of 10 mg three times a day, costs approximately $220 per year.

Metoprolol

Standard dosage	1 to 2 mg/kg/d by mouth administered in two divided doses, with a maximum dosage of 6 mg/kg/d.
Cost/cost-effectiveness	A 50-mg once-daily dose costs $0.90 to $1.25, or $460 per year.

Diuretics

- Diuretics reduce intravascular volume and steer the left ventricle to a more favorable position in its end-diastolic pressure-volume relationship. Adult patients who respond favorably to hemodynamic manipulation appear to have a better prognosis [43,44].
- Hydrochlorothiazide works by inhibiting sodium reabsorption at the distal renal tubules. It is an appropriate and often-prescribed option for combination therapy in the treatment of pediatric hypertension. The loop diuretics are also useful but have more significant side effects.
- *Contraindications*: Use with extreme caution in patients who have experienced hypersensitivity to any diuretic within the same class, patients with sulfonamide allergy, and patients with diabetes mellitus.

Loop diuretics

Furosemide

Standard dosage	0.5 to 2 mg/kg by mouth every 6 to 12 h.
Main side effects	Alkalosis, hyperglycemia, hyperuricemia, hypocalcemia, hypochloremia, hypokalemia, hypomagnesemia, hyponatremia, ototoxicity.
Special points	Patients treated with loop diuretics should have their electrolyte levels monitored periodically because of the aforementioned side effects [5].
Cost/cost-effectiveness	Generic forms are available at a cost of $0.15 per tablet. Additionally, a year's supply of the oral formula at a dosage of 20 mg twice a day costs $250.

Thiazide diuretics

Hydrochlorothiazide

Standard dosage	0.5 to 2 mg/kg/d by mouth in one or two divided doses, with a typical maximum dosage for hypertension of 50 mg/d.
Main side effects	Hyperglycemia, hyperuricemia, hypokalemia, hypomagnesemia, ototoxicity.
Cost/cost-effectiveness	Each 25-mg tablet costs $0.08 to $0.10, making a year of therapy (12.5 mg twice a day) about $40.

Chlorothiazide

Standard dosage	20 mg/kg/d by mouth in two divided doses, with a maximum dosage of 1 g/d.
Cost/cost-effectiveness	Generic tablets are approximately $0.15 per tablet. A regimen of 250 mg twice a day costs $110 per year.

Potassium-sparing diuretics

Spironolactone

Standard dosage	1.5 to 3.3 mg/kg/d orally in divided doses every 6 to 24 h, with a maximum dosage for hypertension of 50 mg/d.
Contraindications	Hyperkalemia.
Main drug interactions	Additive increases in serum potassium may occur with concomitant administration of spironolactone with agents such as potassium supplements, ACE inhibitors, or nonsteroidal anti-inflammatory drugs (NSAIDs).
Cost/cost-effectiveness	At $0.46 per tablet, a year of therapy (25 mg twice daily) costs about $340.

ACE inhibitors

- Reduction of afterload to modulate vascular and ventricular stiffness: Neurohormonal modulation of the renin-angiotensin-aldosterone system is currently the only therapy with an effect on some of the pathophysiologic mechanisms responsible for the increase in vascular and ventricular stiffness [45,46].
- ACE inhibitors have been used with regularity in practice because of their ease of administration, relative lack of side effects, and ample clinical experience.
- *Contraindications*: Contraindications for ACE inhibitors include patients who have experienced hypersensitivity to any agents in the class or who are pregnant. Use with extreme caution in patients with renal artery stenosis, collagen vascular disease, or idiopathic or hereditary angioedema.
- *Main drug interactions*: ACE inhibitors in combination with potassium supplements or potassium-sparing diuretics may cause an additive hyperkalemic effect. Use of ACE inhibitors with NSAIDs in patients with renal impairment may further decrease renal function.
- *Main side effects*: Angioedema, cough, hyperkalemia, neutropenia, rash, and renal function deterioration.

Captopril

Standard dosage	Children: 0.3 to 0.5 mg/kg by mouth typically given every 8 h, titrated upward to a maximum of 6 mg/kg/d in two to four divided doses. Adolescents: 12.5 to 25 mg by mouth given every 8 h, titrated upward to a maximum dosage of 450 mg/d.
Special points	Although captopril is the most widely studied ACE inhibitor in children, it has a shorter half-life than the other commonly used agents in this class of

		medication. The shorter half-life necessitates more frequent dosing, which might have an impact on compliance.
	Cost/cost-effectiveness	Generic forms are available at a cost of about $0.70 per 12.5- or 25-mg tablet. Therefore, 1 year of therapy using a dosage of 12.5 mg every 8 h is approximately $770.

Enalapril

	Standard dosage	Children: 0.1 mg/kg/d by mouth in one or two divided doses, increased to a maximum of 0.5 mg/kg/d. Adolescents: 2.5 to 5 mg/d by mouth, increased as required, with the usual dosage for hypertension 10 to 40 mg/d in one or two divided doses.
	Cost/cost-effectiveness	Enalapril is available as a generic product; a year of therapy with a prescribed dose of 5 mg twice a day costs around $750.

Lisinopril

	Standard dosage	0.07 mg/kg by mouth once daily; with a maximum initial dose of 5 mg titrated up to a maximum total daily dose of 0.61 mg/kg or 40 mg.
	Cost/cost-effectiveness	The average wholesale price is $1.00 to $1.10 per 20-mg tablet.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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••   Of major importance

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